Strathprints Institutional Repository

ChemComm

RSC Publishing

COMMUNICATION

View Article Online
View Journal

Flexible access to conformationally-locked bicyclic morpholines†

Cite this: DOI: 10.1039/c3cc45627g

Received 24th July 2013,
Accepted 15th August 2013

DOI: 10.1039/c3cc45627g

www.rsc.org/chemcomm

Rachael Bogacki,[a] Duncan M. Gill,*[b] William J. Kerr,*[a] Scott Lamont,[c] John A. Parkinson[a] and Laura C. Paterson[a]

A preparatively accessible route to a series of conformationally-locked bicyclic morpholines has been developed. This flexible approach allows for diversification in order for a small array of lead-like scaffolds to be synthesised from readily available key building blocks.

Through an appreciable range of recent endeavours, bridged heterocycles have emerged as desirable synthetic targets within the pharmaceutical industry. More specifically, molecules containing the bispidine (**1**; X = CH_2; Fig. 1) and oxabispidine (**1**; X = O) unit have become increasingly popular due to their evolving range of therapeutic attributes.[1] In relation to this, we have recently disclosed a convenient, modular, and amenable route for the synthesis of a range of chiral, optically-enriched bicyclic oxabispidine structures.[2] Our preparative approach embedded specific key building blocks into the desired molecular scaffold and, in turn, exploited an intramolecular Mannich reaction (IMR) at the heart of our overall synthetic strategy. In this regard, using emerging preparative routes that have allowed the systematic exploration of chemical space, MacLellan and Nelson have very recently established a conceptual framework for analysing, planning, and extending synthetic approaches to diverse lead-like scaffolds,[3] and, indeed, highlighted the applicability of our methods for access to the aforementioned series of flexibly functionalised oxabispidines.[2] Following on from this, based on their potential therapeutic properties and driven by the lack of flexible methods for their preparation,[4] our extended studies in this area have focused on strategies towards a series of differentially-functionalised, strained, and synthetically more challenging bridged bicyclic morpholines, such as **2**. Moreover, our approaches here aimed to further underpin the recently developing concepts around the enhancement of preparative effectiveness aligned with lead-like diversity.[3]

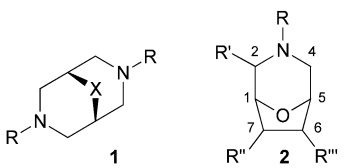


Fig. 1 Bridged bicyclic heterocycles.

Our general preparative approach towards the synthesis of such bridged morpholine units is illustrated in Fig. 2. Key oxazine **5**, bearing a pendant electrophilic unit within the structure, will be selectively cyclised to compounds of structure type **6**; intermediates of type **5** will be synthesised from commercially available glycidol **3** and readily prepared amine acetal **4** as the key starting units. Overall, the synthetic approach described herein allows for diversification at the 2, 6, and 7 positions of the overall bridged morpholine scaffold.

According to this proposed strategy, our initial target molecule was aldehyde **10**. As noted above, the synthesis begins with commercially available glycidol, **3**, which was protected prior to undergoing ring opening with amine acetal **4** (Scheme 1). The addition of sub-stoichiometric quantities of protic acid[5] resulted in efficient formation of core morpholine acetal **8**. Alcohol deprotection and subsequent oxidation, under Swern conditions, delivered the desired aldehyde **10** in high overall yield.

With aldehyde **10** now accessible on good scale, the installation of the additional functionality required for access to the

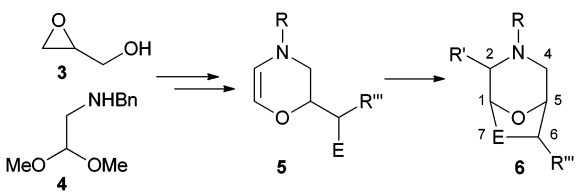
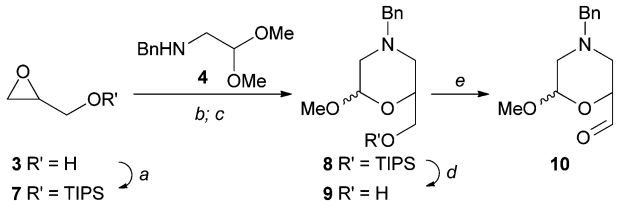


Fig. 2 General preparative approach.

[a] Department of Pure and Applied Chemistry, WestCHEM, University of Strathclyde, 295 Cathedral Street, Glasgow, G1 1XL, Scotland, UK. E-mail: w.kerr@strath.ac.uk; Fax: +44 (0)141 548 4822; Tel: +44 (0)141 548 2959
[b] Department of Chemical and Biological Sciences, University of Huddersfield, Queensgate, Huddersfield, HD1 3DH, England, UK. E-mail: d.m.gill@hud.ac.uk; Fax: +44 (0)1484 472182; Tel: +44 (0)1484 473337
[c] Pharmaceutical Development, AstraZeneca Alderley Park, Macclesfield, SK10 4TG, England, UK

† Electronic supplementary information (ESI) available: Experimental procedures and characterisation data are provided for compounds **4**, and **7–27**. NOESY spectra are provided for compounds **15**, **17**, **24**, **25**, and **27**. See DOI: 10.1039/c3cc45627g



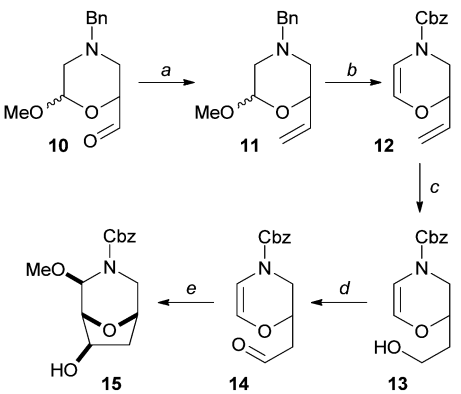
Scheme 1 Preparation of aldehyde **10**. Reaction conditions (a) TIPSCl, imidazole, THF, r.t., 97%; (b) **4**, ethanol, reflux, 100%; (c) *p*-TsOH (40 mol%), 115 °C, 87%; (d) TBAF, THF, 0 °C, 90%; (e) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −60 °C to 0 °C, 98%.

[3.2.1] bridged bicyclic structure **15** was investigated (Scheme 2). Following appreciable Wittig optimisation, Barbier conditions were employed to provide morpholine derivative **11** in an acceptable 59% yield. Subsequently, an amine protecting group switch was carried out in order to facilitate the elimination of methanol and install the desired double bond in **12**.[2a] Hydroboration–oxidation then gave **13**, which, after further oxidation, delivered cyclisation precursor **14**. Following the screening of a variety of Brønsted acids, it was found that *p*-toluenesulfonic acid in the presence of methanol facilitated the key 5-*exo*-trig cyclisation process to deliver the targeted bridged bicyclic morpholine scaffold in a pleasing 71% yield.

Analysis of NMR data revealed that our key cyclisation process was completely diastereoselective, with compound **15** being obtained as a single diastereomer. In order to authenticate the relative stereochemistry, NOESY experiments were performed; interpretation of the nOe interactions established that the bridging oxygen, the methoxy unit, and the alcohol functionality were situated on the same face of the bridged bicyclic structure, as shown in Fig. 3.

With the overall aim of targeting a variety of bridged morpholine units, the developed synthetic approach allows for points of structural diversification to be introduced late in the synthetic pathway, leading to maximised preparative efficiencies. For example, **15** was converted into the corresponding ketone **16** (Scheme 3). Subsequent nucleophilic addition with methylmagnesium chloride produced derivative **17** in a good 72% yield and as a single diastereomer.

With the cyclisation approach to the novel bridged bicyclic morpholine structures established, our studies continued towards the preparation of more heavily substituted analogues. Envisaging that our developed synthetic pathway would be amenable to



Scheme 2 Preparation of bridged bicyclic morpholine **15**. Reaction conditions (a) $BrPPh_3Me$, KHMDS, THF, −78 °C to r.t., 59%; (b) (i) $BnCO_2Cl$, CH_2Cl_2, r.t.; (ii) *p*-TsOH (40 mol%), toluene, reflux, 67%; (c) (i) 9-BBN, THF, r.t.; (ii) 30% H_2O_2, 3 M NaOH, 0 °C, 68%; (d) DMP, CH_2Cl_2, r.t., 75%; (e) *p*-TsOH (10 mol%), MeOH, MeCN, r.t., 71%.

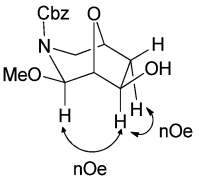
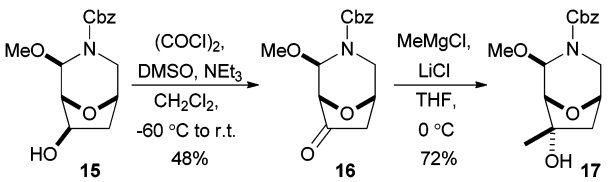


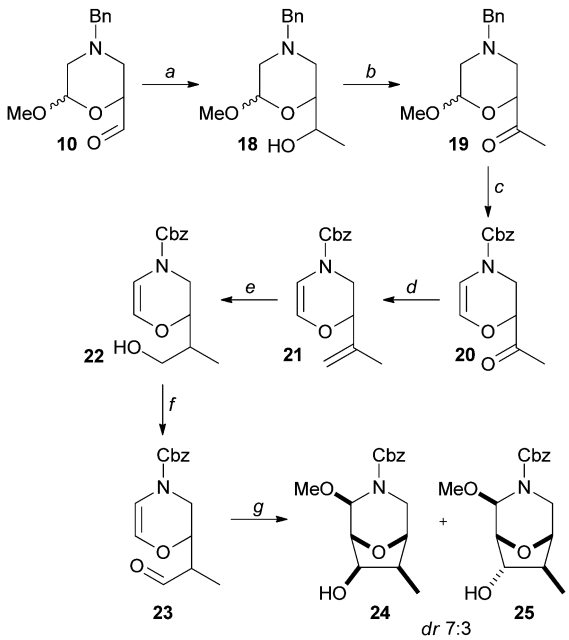
Fig. 3 NMR-based structural elucidation of **15**.

further substitution on the ethylene bridge, the previously synthesised aldehyde **10** was reacted with methylmagnesium chloride to produce alcohol **18** in excellent yield (Scheme 4). Following oxidation, the previously described amine protecting group switch and elimination were carried out to deliver compound **20**. Wittig olefination, followed by a hydroboration–oxidation sequence produced alcohol **22**, which, on further oxidation, delivered cyclisation precursor **23**, all in good yields. We were then pleased to realise that our previously developed cyclisation protocol also facilitated the formation of the alternative bridged morpholine unit, although this time as a mixture of diastereomers (**24**/**25**, 7 : 3 dr).

Evidence from NOESY NMR experiments revealed that within the major diastereomer (**24**) the bridging oxygen, the methoxy unit, the methyl group, and the alcohol moiety were all positioned on



Scheme 3 Preparation of alternative bridged bicyclic morpholines.



Scheme 4 Preparation of bridged bicyclic morpholines **24**/**25**. Reaction conditions (a) MeMgCl, LiCl, THF, 0 °C, 93%; (b) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −60 °C to r.t., 75%; (c) (i) $BnCO_2Cl$, CH_2Cl_2, r.t.; (ii) *p*-TsOH (40 mol%), toluene, reflux, 56%; (d) $BrPPh_3Me$, *t*-BuOK, THF, 0 °C to r.t., 87%; (e) (i) 9-BBN, THF, r.t.; (ii) 30% H_2O_2, 3 M NaOH, 0 °C, 82%; (f) DMP, CH_2Cl_2, r.t., 80%; (g) *p*-TsOH (10 mol%), MeOH, MeCN, r.t., 67%.

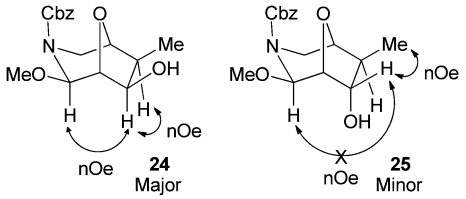


Fig. 4 NMR-based structural elucidation of compounds **24** and **25**.

the same face of the bridged bicyclic morpholine (Fig. 4). Alternatively, analysis of the minor diastereomer (**25**) led to the identification of the structure with epimeric alcohol functionality.

These analyses indicate that the hydroboration of **21** had proceeded in a facially selective fashion. Indeed, the observed mode of reaction is consistent with the studies of and associated models established by Still and Barrish relating specifically to the diastereoselective hydroboration of 1,1-disubstituted allylic alcohols and ethers, where high levels of *anti*-selectivity were found with 9-BBN.[6] This *anti*-stereoselective outcome with substrate **21** to give **22A** is illustrated in Fig. 5. Turning to the further stereochemistry obtained post-cyclisation of **14** and **23**, the transition state depicted in Fig. 6 is proposed. In this model, neighbouring interaction with the bridging morpholine oxygen leads to conformational restriction of the activated aldehyde and, in turn, stereoselectivity in the cyclisation to install the carbinol unit. In the cyclisation of **14** (R = H) only stereoisomer **15** is observed; in contrast, the process with **23** is less selective, potentially due to competing interactions between the R (Me) group and the activated carbonyl, leading to both **24** and **25** (7 : 3). Following cyclisation, methanol approaches on the least hindered face of the resultant iminium ion.

Returning to the preparative studies and in order to extend overall substitution levels, oxidation of **24**/**25** provided ketone analogue **26** (Scheme 5). In a similar process to that described

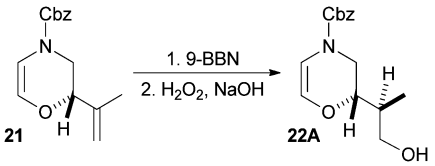


Fig. 5 *anti*-Diastereoselective hydroboration of **21**.

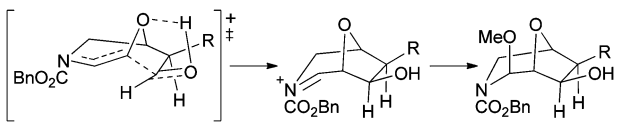
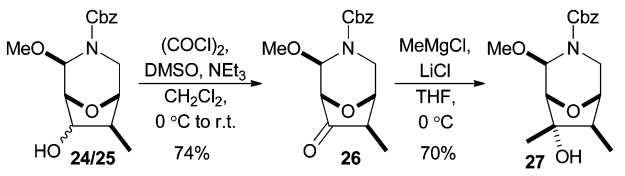


Fig. 6 Proposed model for cyclisation stereoselectivity.



Scheme 5 Preparation of alternative bridged bicyclic morpholines.

with structure **16**, ketone **26** was reacted with methylmagnesium chloride to deliver alcohol derivative **27** as a single diastereomer.

In summary, we have established a preparatively flexible strategy for access to a series of novel bridged morpholine units. Moreover, it is believed that both the use of readily available starting materials and the ability to perform late-stage structural manipulations further enhance the effectiveness of the approach described. Indeed, it is important to highlight that the directing stereocentre within this overall sequence is provided by the glycidol building block (**3**) at the very outset of our synthetic pathway. Accordingly, this overall approach has the potential to enhance the available synthetic strategies towards diverse lead-like scaffolds for application in a range of therapeutic areas. Further studies towards the establishment of associated asymmetric routes are currently on-going within our laboratories.

We would like to thank the EPSRC and AstraZeneca for funding. Mass spectrometry data were acquired at the EPSRC UK National Mass Spectrometry Facility at Swansea University.

Notes and references

1 (*a*) C. Boss, C. Brotschi, B. Heidmann, T. Sifferlen and J. T. Williams, *PCT Int. Appl.*, WO 2013-050938 A1, 2013; (*b*) A. Mazurov, L. Miao, Y.-D. Xiao, D. Yohannes, S. R. Akireddy, S. R. Breining, D. Kombo and V. S. Murthy, *PCT Int. Appl.*, WO 2010-002971 A1, 2010; (*c*) A. Zask, J. A. Kaplan, J. C. Verheijen, K. J. Curran, D. J. Richard and S. Ayral-Kaloustian, *U.S. Pat. Appl. Publ.*, US 2008-251712 20081015, 2009; (*d*) A. Mazurov, L. Miao, Y.-D. Xiao, P. S. Hammond, C. H. Miller, S. R. Akireddy, V. S. Murthy, R. C. Whitaker, S. R. Breining and M. S. Melvin, *PCT Int. Appl.*, WO 2008-057938, 2008; (*e*) M. Furber, L. Alcaraz, J. E. Bent, A. Beyerbach, K. Bowers, M. Braddock, M. V. Caffrey, D. Cladingboel, J. Collington, D. K. Donald, M. Fagura, F. Ince, E. C. Kinchin, C. Laurent, M. Lawson, T. J. Luker, M. M. P. Mortimore, A. D. Pimm, R. J. Riley, N. Roberts, M. Robertson, J. Theaker, P. V. Thorne, R. Weaver, P. Webborn and P. Willis, *J. Med. Chem.*, 2007, **50**, 5882; (*f*) A. Bjore, D. Cladingboel, G. Ensor, A. Herring, J. Kajanus, R. Lundqvist, C. Olsson, C.-G. Sigfridsson and G. Strandlund, *PCT Int. Appl.*, WO 2006-SE688 20060612, 2006; (*g*) C. Chan, J. N. Hamblin, H. A. Kelly, N. P. King, A. M. Mason, V. K. Patel, S. Senger, G. P. Shah, N. S. Watson, H. E. Weston, C. Whitworth and R. J. Young, *PCT Int. Appl.*, WO 2002-GB2586 20020606, 2002; (*h*) G. L. Garrison, K. D. Berlin, B. J. Scherlag, R. Lazzara, E. Patterson, T. Fazekas, S. Sangiah, C.-L. Chen, F. D. Schubot and D. Van der Helm, *J. Med. Chem.*, 1996, **39**, 2559; (*i*) G. S. Smith, M. D. Thompson, K. D. Berlin, E. M. Holt, B. J. Scherlag, E. Patterson and R. Lazzara, *Eur. J. Med. Chem.*, 1990, **25**, 1.

2 (*a*) H. Brice, D. M. Gill, L. Goldie, P. S. Keegan, W. J. Kerr and P. H. Svensson, *Chem. Commun.*, 2012, **48**, 4836; (*b*) D. M. Gill, *PCT Int. Appl.*, WO 2003-045956, 2003.

3 (*a*) P. MacLellan and A. Nelson, *Chem. Commun.*, 2013, **49**, 2383; see also: (*b*) M. Dow, M. Fisher, T. James, F. Marchetti and A. Nelson, *Org. Biomol. Chem.*, 2012, **10**, 17.

4 (*a*) R. A. Brawn, C. R. W. Guimarães, K. F. McClure and S. Liras, *Org. Lett.*, 2012, **14**, 4802; (*b*) H.-Y. Xiao, A. Balog, R. M. Attar, D. Fairfax, L. B. Fleming, C. L. Holst, G. S. Martin, L. M. Rossiter, J. Chen, M.-E. Cvjic, J. Dell-John, J. Geng, M. M. Gottardis, W.-C. Han, A. Nation, M. Obermeier, C. A. Rizzo, L. Schweizer, T. Spires Jr., W. Shan, A. Gavai, M. E. Salvati and G. Vite, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 4491; (*c*) Z. Chen, A. M. Venkatesan, O. D. Santos, E. D. Santos, C. M. Dehnhardt, S. Ayral-Kaloustian, J. Ashcroft, L. A. McDonald and T. S. Mansour, *J. Org. Chem.*, 2010, **75**, 1643; (*d*) F. J. Sayago, J. Fuentes, M. Angulo, C. Gasch and M. A. Pradera, *Tetrahedron*, 2007, **63**, 4695; (*e*) M. S. M. Timmer, M. D. P. Risseeuw, M. Verdoes, D. V. Filippov, J. R. Plaisier, G. A. van der Marel, H. S. Overkleeft and J. H. van Boom, *Tetrahedron: Asymmetry*, 2005, **16**, 177; (*f*) A. Kilonda, E. Dequeker, F. Compernolle, P. Delbeke, S. Toppet, B. Bila and G. J. Hoornaert, *Tetrahedron*, 1995, **51**, 849; (*g*) D. D. Long, N. L. Hungerford, M. D. Smith, D. E. A. Brittain, D. G. Marquess, T. D. W. Claridge and G. W. J. Fleet, *Tetrahedron Lett.*, 1999, **40**, 2195.

5 H. Ito, Y. Ikeuchi, T. Taguchi, Y. Hanzawa and M. Shiro, *J. Am. Chem. Soc.*, 1994, **116**, 5469.

6 W. C. Still and J. C. Barrish, *J. Am. Chem. Soc.*, 1983, **105**, 2487.